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Cadmium and Reproductive Health in Women: A Systematic Review of the Epidemiologic Evidence

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Abstract An evolving body of evidence supports that cadmium, a non-essential heavy metal, may be associated with multiple adverse women's reproductive health outcomes. Our objective was to conduct a systematic review of epidemiologic studies that evaluated cadmium exposure and the following reproductive health outcomes: puberty/menarche, fertility, time to pregnancy, pregnancy loss, preeclampsia, endometriosis, uterine leiomyoma, and menopause. Twenty-two studies were identified based upon our search criteria. Available evidence was inadequate to draw meaningful conclusions for most of the reproductive outcomes studied. The strongest evidence was for a possible association between cadmium and preeclampsia, which was limited to cross-sectional studies. Some evidence, although conflicting, was also observed for fertility related outcomes. This lack of evidence underscores the need for additional research on cadmium and women's reproductive health outcomes.

Keywords Cadmium · Fertility · Endometriosis · Leiomyoma · Menarche · Menopause · Metal · Pregnancy loss · Preeclampsia · Reproduction · Reproductive health · Women · Epidemiologic evidence

Introduction

Cadmium is a non-essential heavy metal with nearly ubiquitous exposure. Cadmium use is associated with refining of zinc, lead, and copper ores, mining, production of cadmium-containing soil fertilizers, plastic stabilizers, pigment production, and nickel-cadmium battery production [1]. Population exposure to cadmium primarily occurs through the diet via consumption of seafood, particularly shellfish, as well as from rice [2, 3] and some is found in leafy green and root vegetables [4]. Uptake of cadmium in tobacco plants leads to concentrated cadmium exposure in cigarette smoke [5] and consequently higher cadmium levels in smokers compared to nonsmokers. In areas where smoking rates are declining, cadmium exposure is subsequently declining [6]. Nationally representative surveys in the US show that levels in women have declined from geometric mean levels of 0.44 μg/g in 1988–1994 to 0.28 μg/g in 2003–2008 [6]. However, because cadmium comes from both natural and anthropogenic activities, exposure remains a public health risk and understanding its potential health effects is important [1]. Cadmium accumulates in the kidney and liver, and as such, both blood and urine are accepted epidemiologic biomarkers of cadmium exposure. Specifically, cadmium in urine represents cumulative exposure in the renal cortex of the kidney [7] generally reflective of exposure over a decade, although there are some recent concerns about the interpretation of urine cadmium concentrations at low-moderate levels [8, 9]. Blood cadmium levels reflect more recent exposures, on the order of several months [1, 10].

Cadmium has been identified as an endocrine disruptor [11]. The toxicological evidence with respect to cadmium's effects on the reproductive system was recently reviewed [12–14]. Cadmium may interfere with hormonal functioning by binding at both the nuclear estrogen receptor [15] and G-protein coupled receptor 30 (GPR30) [16–18] and indirectly by P450 side-chain cleavage or through the low density lipoprotein receptor [19, 20] thus, cadmium may also be involved in the etiology of hormonally sensitive health outcomes and diseases. Experimentally, cadmium has shown effects on

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estrogenic activity [15, 21–24], including toxic effects to the ovary [21, 25–27]. Together with estrogen, cadmium increased estrogen receptor alpha mRNA expression beyond either estrogen or cadmium alone [20]. Further, cadmium may contribute to disease processes by altering the balance of oxidative stress [28]. The increasing evidence on human health effects among non-occupationally exposed populations, including cancer and cardiovascular disease [29, 30] hinges upon such effects at environmental levels of exposure.

Our objective was to systematically review the epidemiological evidence on the association between cadmium and women's reproductive health, specifically considering puberty/menarche, reproductive hormones, fertility, pregnancy loss, preeclampsia, uterine leiomyoma, endometriosis, and menopause among individuals non-occupationally exposed to cadmium.

Methods

This systematic review process was conducted under the criteria provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [31], except the evaluation for possible bias and quality of evidence, which were not evaluated in the current paper. We searched in PubMed for relevant, recent, studies published from 2003 through October 31, 2013, using the following combination of Medical Subject Heading (MeSH) search terms and text words: "cadmium" and each of the following terms separately, "puberty", "reproductive hormones", "fertility", "pregnancy loss", "preeclampsia", "uterine leiomyoma", "endometriosis", or "menopause," with additional terms as outlined in Table 1. Inclusion criteria encompassed original epidemiologic research articles that measured cadmium exposure using biomarkers.

Two investigators (SR and AZP) independently reviewed each of the 254 papers and selected 22 papers applying the following exclusion criteria: a) lack of original research, b) not a human study, c) case reports, and d) no cadmium exposure levels from biological tissues (i.e., environmental assessment of cadmium exposure) as outlined in Fig. 1. For studies that analyzed the same population for the same health endpoints, we selected either the most recent publication or the largest sample size. Relevant characteristics of all included studies are summarized in Tables 2, 3, and 4.

Table 1 Search strategy for women's reproductive health outcomes and cadmium

Database	PubMed
Date	September 10, 2013 to October 31, 2013
Time frame	Papers published between 2003-2013
Strategy	The reproductive health terms (#1 to #7) were each combined with the terms cadmium (#8) and women (#9)
#1. Puberty	Puberty, menarche
#2. Reproductive hormones	Follicle stimulating hormone, gonadotropin, estrogen, progesterone, ovulation, anovulation
#3. Fertility	Fertility, infertility, fecundity, IVF, in-vitro fertilization, time to pregnancy
#4. Pregnancy loss	Spontaneous abortion, miscarriage, pregnancy loss
#5. Uterine leiomyoma	Fibroids, uterine leiomyoma
#6. Preeclampsia	Pre-eclampsia, eclampsia, pregnancy-induced hypertension
#7. Endometriosis	Endometriosis
#8. Cadmium	Cadmium
#9. Women	Women, girl, female

Reproductive Health

Puberty/Menarche

Earlier puberty is a risk factor for breast cancer and is a public health concern because of its association with increased risk of metabolic syndrome, diabetes, cardiovascular disease, and obesity [32]. On the other end of the spectrum, delayed pubertal development is considered a risk factor for osteoporosis [33]. Furthermore, the timing of pubertal development and menarche has shifted over the past several decades, as breast development and menarche are occurring earlier than in the past, demonstrating a secular trend [34]. Some have highlighted endocrine disrupting chemicals, including metals, as a possible contributing factor to this shift in reproductive development [35].

One study met our inclusion criteria on cadmium and puberty or menarche in girls (Table 2). National Health and Nutrition Examination Survey (NHANES) data (1988–1994) were used to evaluate the association of urinary cadmium with reproductive hormones inhibin B and luteinizing hormone among 705 girls aged 6–11 [36]. The findings suggest that in the context of elevated blood lead (>5 μg/dl), higher urinary cadmium levels (0.27–3.38 ng/ml) were associated with decreased inhibin B levels, suggesting a link to pubertal delays in adolescent girls [36]. However, this study was limited by several factors. The study was cross-sectional and therefore was unable to clearly establish the temporal relationship between metals and pubertal development. Further, the models were not adjusted for age, a major determinant of cadmium levels in urine and pubertal development and therefore. Confounding by age is thus plausible.

These cross-sectional results are intriguing and highlight the paucity of research regarding the relationship between cadmium and pubertal development in girls. There is a need

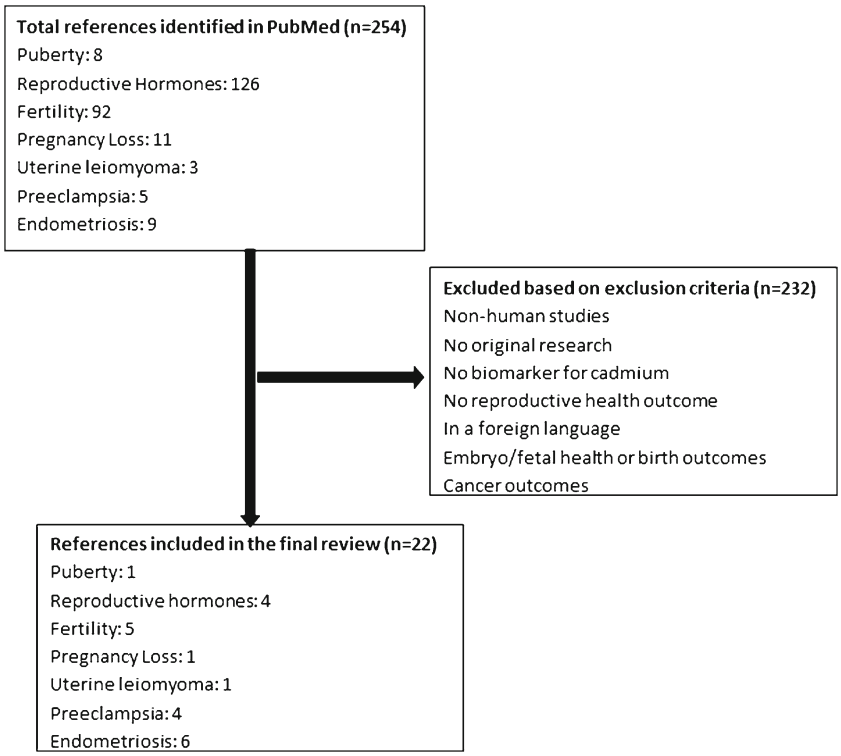

Fig. 1 Flow diagram of the study selection process

for additional, particularly prospective research to understand the possible role of cadmium on pubertal development in girls.

Menstrual Cycle/Reproductive Hormones

Reproductive hormones are important biological signals and play a role in the etiology of cancer and heart disease, among other health conditions [37, 38]. Cadmium has been shown to play a role in modification of hormone levels experimentally, as recently reviewed by Iavicoli et al. [21], and may affect the hypothalamic-pituitary-gonadal axis (HPG) at multiple levels [13].

Four studies met our inclusion criteria using the search terms described in Table 1 [39–42] (Table 2). The studies were conducted in premenopausal women from New York State [39, 40], a US representative sample of perimenopausal women [41], and postmenopausal Japanese women [42]. The sample sizes ranged from 164 to 1050. Cadmium was measured in blood in the premenopausal women but in urine in the peri- and postmenopausal women. Estrogen, follicle stimulating hormone, luteinizing hormone, and progesterone as well as ovulation were the outcomes of interest in the studies in premenopausal women. Cadmium was associated with increased estrogen [39] and declines in FSH [40] in premenopausal women. However, among perimenopausal women with BMI ≥27, cadmium was associated with increased FSH [41]. Testosterone was positively associated with cadmium in postmenopausal women [42]. These studies suggest that menopausal status plays a role in the relationship between cadmium and reproductive hormones but additional research is necessary.

Additional studies at environmentally relevant levels of exposure are needed to confirm the possible role of cadmium in altering reproductive hormone function in women across their reproductive years and the menopausal transition. Although preliminary evidence suggests that cadmium could affect hormone levels, additional research with well-timed collection of reproductive hormone concentrations and exposure assessment will be necessary. Timing of measurements is particularly important given the high variability of reproductive hormones throughout the menstrual cycle in premenopausal women, as well as the current paucity of knowledge regarding the timing or threshold of exposure to cadmium (e.g., acute vs. chronic) and its effects on the various levels of the HPG axis.

Fertility

Infertility, defined as the inability of couples to become pregnant after 12 months of regular unprotected sexual intercourse [43] affects an estimated 3 to 26 % percent of the population [44–46]. Cadmium may affect fertility and fecundity via alterations in reproductive hormones, discussed above, or through oxidative stress and inflammatory pathways. Our review identified five studies that met our inclusion criteria with regard to cadmium and fertility outcomes [47••, 48, 49••, 50, 51]. Two evaluated time to pregnancy among healthy couples, and three evaluated fertilization and ongoing

Table 2 Summary of cadmium exposure and reproductive hormones, fecundity, pregnancy loss, and pubertal development

Endpoint	Study, year	Study type	Population	No. of cases/ non-cases	Mean age (or range in yrs)	Cadmium biomarker	Exposed vs. reference	Endpoint ascertainment	Primary outcome	Adjustment factors
Reproductive hormones	Jackson 2011 [39]	Cohort	Women in New York, US	252	27	Blood	Per 1 μg/l increase	Biomarker	Estradiol RR=21 % (−2.9, 49.9)	Age, race/ethnicity, lead and mercury
Reproductive hormones	Pollack 2011 [40]	Cohort	Women in New York, US	252	27	Blood	Tertile 1: 0.03–0.23 μg/L; Tertile 2: 0.24–0.36 μg/L; Tertile 3: 0.37–3.10 μg/L	Biomarker	Mean difference FSH 1^{st} vs. $2^{n:d}$ −10.0 (−17.3 to −2.5) 1^{st} vs. $3^{rd:}$ −8.3 (−16.0 to 0.1)	Age, race, and BMI
Reproductive hormones	Gallagher 2008	Cross-sectional	US women	1050 perimenopausal women	47	Urine	Continuous	Biomarker	0.45 (0.06, 0.83) among BMI ≥27 kg/m^2 ; 0.61 (0.13, 1.09) among BMI <27	Serum lead, osteoporosis treatment, race, age, smoking status, hormonal treatment, medical or surgical amenorrhea, income, multiparity, and in the perimenopausal subgroup, birth control
Reproductive hormones	Nagata 2005 [42]	Cross-sectional	Postmenopausal Japanese women	164	59	Urine	Tertile 1: <2.00 μg/g creatinine Tertile 2: 2-<3.00 μg/g creatinine Tertile 3: ≥3.00 μg/g creatinine vs.	Serum biomarker	3^{rd} vs. 1^{st} tertile mean estrone 21.5 (16.3-28.5) pmol/L vs. 17.8 (13.3-22.9); DHEAS 2,592 (2,242-3,019) nmol/L vs.1,971 (1,700-2,287); testosterone 0.32 (0.27-0.37) vs. 0.25 (0.21-0.29) nmol/L	Age and BMI
Fecundity	Louis 2012 [49••]	Prospective cohort	US Couples from Michigan and Texas	501	30	Blood	SD 0.31 μg/l increase in blood cadmium	Home pregnancy test	Fecundability OR=0.78 (0.63-0.97)	Age, body mass index, cotinine, parity, serum lipids, study site
Fecundity	Bloom 2011 [48]	Prospective cohort	US women living in New York state	99	30	Blood	1.00 μg/L increase	Home pregnancy test	0.32 (−0.19, 0.83)	Age, parity, groupings of PCB congeners, serum lipids, frequency of intercourse during the fertile window, and smoking and alcohol standardized to a 28-day cycle
Pregnancy after IVF	Al-Saleh 2008 [50]	Cross-sectional	Women undergoing IVF in Saudi Arabia	302 not pregnant cases/ 203 pregnant controls	32	Follicular fluid and blood		Medical record		Women's age, husband's age, BMI, age when menstruation started, days of menstrual cycle, duration of living in the current province, duration of living in the former province, current province of living, former province of living, women's education, husband's education, women's working status, total family income, husband's smoking status and drinking caffeine soft drinks

Table 2 (continued)

Endpoint	Study, year	Study type	Population	No. of cases/ non-cases	Mean age (or range in yrs)	Cadmium biomarker	Exposed vs. reference	Endpoint ascertainment	Primary outcome	Adjustment factors
Fertilization after IVF	Bloom 2012 [47••]	Cross-sectional	Women undergoing IVF in California	46	35.6	Follicular fluid	N/A	Medical record	RR=8.94, (1.32–60.49)	Age, cigarette smoking, and race/ethnicity
Clinical and biochemical pregnancy after IVF	Bloom 2012 [47••]	Cross-sectional	Women undergoing IVF in California	26	38	Blood and urine	1 μg/l increase in blood cadmium;	Medical record	Clinical pregnancy RR=0.06, (0.01–0.51); Biochemical pregnancy RR=0.67 (95 % CI 0.48–0.92)	blood Pb, blood Hg, age, race and smoking
Pregnancy loss	Ajayi et al. 2012 [58]	Cross-sectional	Pregnant women in Ibadan, Nigeria	35 history of 3 spontaneous abortions/34 no history of prior loss	30	Blood	4.58±0.77 μg/dl among women with history of 3 spontaneous abortions vs. 2.49±0.09 μg/dl among women with no such history	N/A	N/A	N/A
Pubertal development	Gollenberg et al. 2010 [36]	Cross-sectional	Peripubertal US girls	705	6-11	Urine	Tertiles (exact cutpoints not specified)	Biomarker	Low Pb (< 5 μg/dL) and low Cd (first and second tertiles vs. High Pb and 3rd tertile cadmium (n=260): inhibin B decreased β=−0.52; 95 % CI, −0.09 to −1.04	BMI, race/ ethnicity census region, and poverty income ratio

pregnancy rates among couples undergoing in vitro fertilization (IVF). Of note is that cadmium levels were measured in urine, blood [48, 49••], and follicular fluid [47••, 50, 51] when evaluating effects on fertility. Follicular fluid is a particularly biologically relevant measure of exposure for reproductive endpoints due to its proximity to endometrial tissues, as well as its direct contact with follicular cells responsible for synthesizing and secreting ovarian hormones which communicate in both a paracrine and endocrine manner with the entire HPG axis.

Two prospective studies in the US examined time to pregnancy among healthy couples trying to conceive [48, 49••] (Table 2). Both studies showed inconsistent findings. Among 80 women aged 18–34 from New York state who were followed prospectively while trying to conceive for up to 12 months or until becoming pregnant, blood cadmium (geometric mean level 1.63 μg/L) was not associated with time to pregnancy, although there was a non-statistically significant 13.74 % increase in probability of a positive pregnancy test for each 1.00 μg/L increase in Cd [48]. In contrast, longer time to pregnancy was associated with blood cadmium levels (fecundability odds ratio 0.78 (95 % CI 0.63-0.97) in a second prospective cohort study of 501 couples trying to conceive for up to 12 months, after adjustment for age, body mass index, cotinine, parity, serum lipids, and study site [49••]. In both of these studies, potential confounders were considered and all metals values were reported, regardless of limit of detection (LOD), a strategy that minimizes bias [52]. The conflicting evidence of these reports may be due to difference in cohort size, cohort characteristics, or unmeasured factors, but such differences highlight the need for further high quality research to identify the role of cadmium in time to pregnancy.

Three studies focused on in vitro fertilization, with mixed findings [47••, 50, 51] (Table 2). One study in Saudi Arabia reported that follicular fluid cadmium levels were associated with increased odds of fertilization while blood cadmium levels were not [50]. The mean follicular cadmium level was 0.34 μg/L (range<LOD–9.45 μg/L) in women who achieved fertilization as compared to 0.24 μg/L (range<LOD −0.90 μg/L) among those without fertilization. Blood cadmium levels were about double follicular levels and the two were highly correlated (0.59 $p<0.0001$). Pregnancy was not associated with cadmium levels. A study measuring follicular fluid cadmium levels among 46 women undergoing IVF in San Francisco similarly found a positive association between oocyte fertilization and follicular fluid cadmium [51]. However, the variability of follicular cadmium was low due to nearly half of the values being below or near the LOD. Additional endpoints considered in this study included oocyte maturity, biochemical pregnancy, and clinical pregnancy, which were not significantly associated with follicular fluid cadmium levels [51]. Blood and urine cadmium levels were also measured in the same group of women. Biochemical 0.18 (95 % CI: 0.03, 0.94) and clinical pregnancy risk 0.06 (95 % CI: 0.01, 0.51) were associated with a 1 g/μL increase in blood cadmium [47••]. Blood and urinary cadmium levels in this small study were comparable to NHANES levels in the US. Collectively, the three IVF studies suggest that while cadmium in follicular fluid may be related to in vitro oocyte fertilization positively, it may act through different mechanisms systemically that ultimately result in diminished pregnancy rates. These studies, however, need to be interpreted cautiously due to their small sample sizes.

In summary, of the two prospective pregnancy studies in cohorts trying to conceive without assisted reproductive technology, one found no association between cadmium and fecundity [48] while one found a statistically significantly reduced fecundability odds ratio with increasing cadmium levels in women [49••] (Table 2). Clearly, more prospective pregnancy studies are needed to elucidate the potential association between cadmium and longer time to pregnancy among couples trying to conceive without fertility treatment. With respect to couples undergoing IVF, both available studies that measured follicular fluid cadmium levels, found a positive relationship between cadmium levels in follicular fluid and fertilization. However, cadmium in blood was associated with a reduced risk of biochemical and clinical pregnancy. These opposing findings by culture media underscore the need for future research on populations of women undergoing assisted reproductive therapy to clarify the relationship between cadmium and fertility in this important sub-population.

Pregnancy Loss

Pregnancy loss, or miscarriage, affects approximately one third of all conceptions [53] and 10-15 % of clinically recognized pregnancies [54]. Cadmium may affect pregnancy loss via effects on endocrine pathways or via the promotion of oxidative stress, which has been linked to adverse reproductive health [55]. Specifically, cadmium may reduce the body's natural antioxidant capacity, for example, by depleting glutathione [56].

Two studies were found evaluating the association between cadmium and pregnancy loss, though one of the studies used a proxy of residence in a region polluted with cadmium as a proxy for individual exposure (Table 2). Differences in the percent of married women with pregnancy losses reported in their first or second pregnancies in the polluted as compared to the control region (10 vs. 2.8 %) were statistically significant but due to reliance on a proxy of exposure the study was not eligible for inclusion in the present review [57]. The study that met the inclusion criteria measured cadmium levels in serum in 69 pregnant women who were recruited from a clinic between 0–20 weeks of gestation in Ibadan, Nigeria [58]. Women with a self-reported history of recurrent (defined as

Table 3 Summary of cadmium exposure and preeclampsia

Study, year	Study type	Population	No. of cases/ non-cases	Mean age (or range in yrs)	Cadmium biomarker	Definition of exposure vs. reference group	Endpoint ascertainment	Relative risk or mean estimate (95 % CI)	Adjustment factors
Kolusari 2008 [62]	Clinical convenience sample	Women from Turkey	47/48 preeclamptic/ healthy pregnant, 50 healthy non-pregnant	27	Serum	Comparison of mean levels in preeclamptic women, healthy pregnant women, and non-pregnant women	Medical record	Mean blood cadmium levels preeclamptic 0.33±0.20 μg/L vs. healthy pregnant 0.29±0.27 μg/L vs. non-pregnant 0.29±0.21 μg/L ($p<0.05$)	N/A
Kosanovic 2002 [61]	Clinical convenience sample	3rd trimester pregnant women in Belgrade, Yugoslavia	23 /37	29	Blood	Compared cadmium level in smokers vs. nonsmokers between hypertensive and normotensive women	Medical record	Blood cadmium in nonsmoking normotensive 0.8±0.3 μg/L vs. nonsmoking hypertensive 1.3±0.1 μg/L ($p<0.01$); smoking normotensive 2.2±1.1 μg/L vs. smoking hypertensive 1.9±0.6 μg/L ($p>0.05$)	N/A
Vigeh 2006 [63]	Case–control study	3rd trimester pregnant women in Tehran, Iran	31/365	15-49	Blood	Compared blood levels in preeclamptic to non-preeclamptic women	Medical record	Mean level in preeclamptic 0.54±0.31 μg/L vs. non-preeclamptic 0.50±0.30 μg/L	BMI, nulliparity, education, multiple gestations, pregnancy weight gain, age, hematocrit, umbilical cord blood and mother blood metals: lead, copper, magnesium, zinc, antimony, manganese, mercury, cobalt
Dawson 1999 [64]	Clinical convenience sample	3rd trimester pregnant women	29/101	N/A	Amniotic fluid	Compared healthy pregnant women to preeclamptic women at 33–36 weeks gestation and at 37–40 weeks gestation	Medical record	Mean cadmium level 33–36 weeks gestation normotensive 940±40 μg/l vs. hypertensive 1000±270 μg/l ($p>0.05$); 37–40 weeks normotensive 900±100 μg/l preeclamptic 106±190 μg/l ($p<0.05$)	N/A

three or more) pregnancy losses had mean blood cadmium levels of .46 μg/L while controls (women without a history of recognized pregnancy loss) had lower mean cadmium levels of 0.25 μg/L ($p<0.05$). No other studies on pregnancy loss were identified.

As very little human data were available, additional prospective studies at environmentally relevant levels of cadmium exposure are needed to elucidate a possible association between cadmium and pregnancy loss. It is important to ascertain both early and clinical pregnancy losses as early losses may frequently be missed if a pregnancy test was not taken early enough. Therefore, identification of cases is problematic, and reliance on retrospective self-report of pregnancy loss is often not adequate. Therefore, prospective studies with careful evaluation of pregnancy loss and its timing in relation to cadmium exposure are needed.

Preeclampsia

Preeclampsia is characterized by hypertension and proteinuria in pregnancy and occurs in approximately 5–10 percent of all pregnancies [59]. Preeclampsia is associated with significant morbidity for the infant and mother and has largely unknown etiology. An earlier review introduced the hypothesis that cadmium was involved in the etiology of preeclampsia [60].

Our review identified five articles on preeclampsia, eclampsia, or pregnancy-induced hypertension, three of which met our inclusion criteria [61–63]. The studies were cross-sectional and limited their analysis to evaluating a difference in mean cadmium levels across women with and without preeclampsia or hypertension without adjustment for relevant confounders (Table 3). One cross-sectional study of 60 pregnant women in Belgrade, Yugoslavia measured cadmium levels in maternal blood and found that cadmium levels were more than two-fold higher in hypertensive nonsmokers compared with normotensive nonsmokers (1.9 μg/L vs. 0.8 μg/L, $P=0.001$) [61]. However, among smokers, cadmium levels did not significantly differ (normotensive: 2.2 μg/L vs. hypertensive 1.9 μg/L) from one another, with both groups having levels comparable to those detected among hypertensive nonsmokers. This study did not attempt to account for potential confounding factors but rather only assessed a difference in means by smoking and hypertension status. A cross-sectional study of 145 women in Turkey measured cadmium in blood and found that mean levels were significantly higher in preeclamptic women ($n=47$, 0.33 μg/L) compared with healthy pregnant women ($n=48$, 0.29 μg/L) [62]. However, a case–control study in Iran measured cadmium in blood and did not find differences in mean levels between preeclampsia cases (0.54 μg/L) and controls (0.50 μg/L) [63]. Although published prior to 2003, one additional cross-sectional study measured cadmium levels in third trimester amniotic fluid in 101 normotensive pregnant women and 29 preeclamptic women [64]. The authors divided the samples into early (33–36 weeks) and late (37–40 weeks) third trimester samples and compared mean cadmium levels by preeclampsia vs. normotensive status within these groups. Amniotic fluid cadmium levels did not differ in the early third trimester group, but cadmium levels were higher in the amniotic fluid of preeclamptic women in late third trimester (106 mg/dl vs. 90 mg/dl) [64]. This stratification across the late third trimester is problematic and could induce bias because treatment for preeclampsia often involves inducing labor and delivery, hence resulting in an earlier delivery. Therefore, the severity of preeclampsia may differ across the groupings with later third trimester pregnancies likely having less severe disease than the earlier group.

All of the studies identified were cross sectional, did not utilize incident cases of preeclampsia, and were unable to evaluate the temporality of cadmium exposure levels and development of pregnancy-related hypertension. Together with the strong evidence of an association between cadmium and hypertension in adults [65] likely driven by cadmium's pro-atherogenic activity in the circulatory system [66], these findings are suggestive that cadmium may play a role in pregnancy-related hypertensive disease, including preeclampsia, but additional research is needed to clarify these associations. In particular, prospective studies with incident identification of pre-eclampsia cases are necessary.

Uterine Fibroids

Uterine leiomyoma (fibroids) are noncancerous tumors in the myometrium and are the leading indication for gynecologic surgery. Fibroids cause reproductive dysfunction and pelvic pain [67]. Further, in the US, fibroids cost between $6 to $34 billion per year due to direct medical expenses and lost productivity [68]. Few risk factors for fibroids are known, apart from black race and age [69]. However, cadmium's estrogenic properties are thought to contribute to the etiology of fibroids.

One large study compared cadmium levels in blood between women with and without self-reported uterine fibroids ($n=1425$) and found no association [70] (Table 4). This was a nationally-representative cross-sectional study based upon self-report of uterine fibroids in NHANES. Self-report of fibroids is problematic because many women with fibroids are unaware of their condition [71]. Further, 25 % of women included in the study had cadmium levels below the limit of detection (0.3 μg/L).

Overall, the evidence with respect to uterine leiomyoma and cadmium is inadequate to draw conclusions. Additional research on this prevalent gynecological health endpoint with largely unknown etiology in relation to cadmium exposure is needed.

Table 4 Summary of cadmium exposure, uterine leiomyoma, and endometriosis

Endpoint	Study, year	Study type	Population	No. of cases/ non-cases	Mean age (or range in yrs)	Cadmium biomarker	Exposed vs. reference	Endpoint ascertainment	Outcome	Adjustment factors
Uterine leiomyoma	Jackson 2008 [70]	Cross-sectional	US women NHANES 1999-2002	114/1308	20-49	Blood	Tertile 1: <0.3 μg/L Tertile 2: 0.3-0.4 μg/L Tertile 3: 0.5–8.5 μg/L	Questionnaire	Mean level in UL cases vs. non-UL cases 0.5–8.5 μg/l vs. <0.3 μg/l RR 1.04 (0.60-1.80)	Lead, mercury, race/ethnicity, smoking status at diagnosis, use of birth control pills prior to diagnosis and age
Endometriosis	Pollack 2013 [81]	Matched cohort	US women from San Francisco, California, and Salt Lake City, Utah	473 operative 131 population	18-44	Blood and urine	Tertile1: <21 μg/L Tertile 2: 0.21-0.36 μg/L Tertile 3: ≥37 μg/L	Surgical visualization and MRI	Blood cadmium in operative cohort OR=0.55 (0.31-0.98); 3rd vs 1st tertile cadmium in population cohort blood OR= 0.14 (95 % CI: 0.01, 1.58); urine OR= 0.12 (0.01, 2.73) 3rd vs. 1st tertile in operative cohort blood OR=0.55 (0.31, 0.99); urine OR=0.66 (0.33, 1.29) Additional concurrent adjustment for other significant metals 3rd vs. 1st tertile blood OR= 0.52 (95 % CI 0.29, 0.94)	age (years), body mass index (kg/m2), smoking (yes/no), site (CA/UT), race (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Islander/Native American, other), vitamin use (yes/no), urine creatinine (restricted to urinary metals), and parity conditional on gravidity (never pregnant/pregnant without births/ pregnant with births)
Endometriosis	Silva 2013 [78]	Case–control study	Women from Sri Lankan	50/50	33	Blood	0.7 μg/l cases vs. 0.8 μg/l controls	Surgical visualization	N/A	N/A
Endometriosis	Jackson 2008 [70]	Cross-sectional	US women NHANES 1999-2002	61/1362	20-49	Blood	0.5–8.5 μg/l vs. <0.3 μg/l	Questionnaire	OR=3.39 (1.37-8.40)	Lead, mercury, race/ethnicity, smoking status at diagnosis, use of birth control pills prior to diagnosis and age
Endometriosis	Itoh 2008 [77]	Case–control study	Infertile Japanese women	54/74	20-45	Urine	0.707-7.92 μg/g vs. 0.184-0.389 μg/g	Medical record	0.86 (0.30-2.49)	Average menstrual cycle, body mass index, smoking status
Endometriosis	Heilier 2006 [80]	Case–control study	Women from Belgium	119/25	30	Blood and Urine	0.3 μg/g creatinine across deep, peritoneal, both endometriosis types, and controls; blood 0.4 μg/l for deep, peritoneal and controls, 0.3 μg/l for both endometriosis types	Medical record	N/A	N/A

Table 4 (continued)

Endpoint	Study, year	Study type	Population	No. of cases/ non-cases	Mean age (or range in yrs)	Cadmium biomarker	Exposed vs. reference	Endpoint ascertainment	Outcome	Adjustment factors
Endometriosis	Heilier 2004 [79]	Case–control study	Women from Belgium	Peritoneal endometriosis 25/ Deep endometriosis 13 /Controls 21	30	Blood and Urine	Geometric mean urinary cadmium levels: peritoneal endometriosis 0.25 [SD 1.50], deep endometriosis 0.29 [SD 1.76] and controls 0.26 [SD 1.46] μg/g creatinine; geometric mean blood levels 0.1 for all groups	Surgical visualization	N/A	N/A

Endometriosis

Endometriosis is a disease that affects an estimated 6-11 % of reproductive-aged women and is often associated with infertility [72]. Endometriosis is characterized by a growth of endometrial glands and stroma outside the uterus [73]. However, while recognized as an estrogen-sensitive disease, endometriosis risk factors are poorly understood. The few established risk factors include Caucasian race, lean body type, and history of infertility [74, 75]. Cadmium may play a role in the etiology of endometriosis via its estrogenic properties [76] or through modification of oxidative stress [55].

We identified six epidemiological studies (Table 4). The studies were conducted in Belgium, Japan, Sri Lanka, and the US. Cadmium was measured in urine in two of the studies [77, 78], in blood in one study [70] and in both in three studies [79–81]. Endometriosis was defined by surgical visualization [77–80], and self-report [70]. Of the six studies, only one, a cross-sectional nationally-representative study in the US based upon data from NHANES found that cadmium was positively associated with endometriosis diagnosis. After adjustment for age, race/ethnicity, use of birth control pills prior to diagnosis, and smoking status at diagnosis, the estimated odds of endometriosis comparing the highest (0.5–8.5 μg/L) to the lowest tertile of exposure (<0.3 μg/L) was 3.39 (95 % CI 1.37-8.40) [70]. One study among 473 women from Salt Lake City, Utah and San Francisco, California, found a reduced odds of incident, surgically visualized, endometriosis associated with blood cadmium >0.37 μg/L (aOR = 0.55; 95 % CI: 0.31, 0.98) when compared with the lowest exposure tertile (<21 μg/L). However, urinary cadmium was not associated with endometriosis in this study [81]. The remaining four studies found no association between cadmium and endometriosis. Of these, three case–control studies did not attempt to adjust for potential confounding factors or utilize statistical modeling and analysis was limited to a comparison

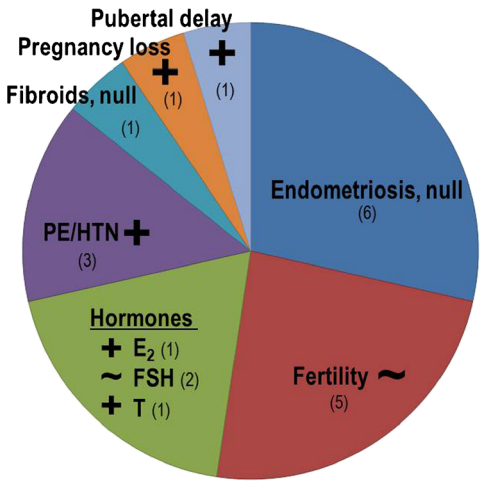

Fig. 2 Summary of the evidence on women's health endpoints in relation to cadmium exposure

of geometric mean levels, in which no differences were detected [78–80]. One remaining case–control study was restricted to an infertile population and adjusted for average menstrual cycle length, body-mass index, and smoking status, and similarly, found no association between endometriosis and cadmium [77].

The weight of the evolving though limited body of evidence suggests that cadmium is not associated with endometriosis, with one study supporting a positive association, another study supporting a negative association, and four null studies. The one study that found a positive association between cadmium and endometriosis relied on self-report of endometriosis and measured cadmium levels in blood [70], which may not correspond to exposure at the time of endometriosis development. A negative association between blood cadmium and endometriosis [81] may be explained if cadmium lowers circulating estrogen levels, as endometriosis is an estrogen-sensitive disease. However, understanding cadmium potential effects on estrogen promotion of endometriosis requires further investigation. Most of these studies were cross-sectional without incident ascertainment of endometriosis cases. Prospective studies are needed to confirm the lack of association between cadmium exposure and incident endometriosis.

Menopause

Our review did not find any papers on cadmium and menopause specifically. A review on cadmium and menopause found a range of health effects affecting women around the time of menopause but noted the lack of data available with respect to timing of menopause and cadmium [82]. This lack of research on a potential role for cadmium in the timing of menopause underscores a need for further research on this topic.

Conclusions

Overall, cadmium may be considered a reproductive toxicant in women with respect to some reproductive health outcomes, with the greatest body of evidence existing for pregnancy-related hypertension and preeclampsia (Fig. 2). However, there is inadequate evidence to draw conclusions regarding health risks from cadmium exposure and several important endpoints. These include pubertal development, reproductive hormones, fertility, pregnancy loss, and menopause. Taken together, this review underscores the need for additional research into reproductive health effects of cadmium exposure. This is particularly important as women may be more susceptible to health effects of cadmium and consistently have higher exposure levels compared to men [83].

This review reveals a need for prospective studies that appropriately address limits of detection and confounding issues (e.g., current and past smoking) to better establish temporality between cadmium exposure and reproductive health outcomes in women. Improving the assessment of exposure measurement to appropriately address limits of detection issues, and to better understand how the media where cadmium is measured may play a role to better target blood, urine, or follicular fluid in future studies. Assessing women's health outcomes can be complicated and many studies relied upon self-report or clinically ascertained samples. Such methods are limited when individuals are either not aware of their diagnosis or do not seek care. Statistical limitations are a further drawback of many of the studies included in this review. Specifically, the lack of attempt to address confounding or analysis beyond a comparison of mean levels is a shortcoming that should be improved in future studies. In sum, research on women's health in relation to cadmium exposure is important given nearly ubiquitous exposure to cadmium in the population and some but not definitive evidence regarding cadmium exposure and women's reproductive health related outcomes.

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Compliance with Ethics Guidelines

Conflict of Interest Anna Z. Pollack, Shamika Ranasinghe, Lindsey A. Sjaarda, and Sunni L. Mumford declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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